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concl'd*
72. A method for the treatment of human mammary carcinoma comprising administering to a human in need thereof a cell line containing a DNA construct comprising a therapeutic gene laced under transcriptional control of an WAP regulatory sequence, wherein the therapeutic gene is expressed and the human mammary carcinoma is treated.
73. A method for the treatment of human mammary carcinoma comprising implanting into a human in need thereof either in or nearby the site of the tumor a capsule encapsulating a cell line containing a construct comprising a therapeutic gene placed under transcriptional control of an WAP regulatory sequence, said capsule comprising a porous capsule wall surrounding said cell line, said porous capsule wall being permeable to the heterologous polypeptide or the viral particles produced by said cells.
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### REMARKS

#### Claim amendments

The claims have been amended to recite a set of claims directed to compositions comprising the MMTV regulatory sequence and uses thereof (Claims 1-40) and a set of claims directed to compositions comprising the WAP regulatory sequence and uses thereof (Claims 41-73). As amended, Applicants claim a retroviral construct comprising a heterologous gene placed under the transcriptional control of an MMTV regulatory sequence (Claims 1-11) or a WAP regulatory sequence (Claims 53-59); a recombinant retroviral particle produced from the retroviral vectors (Claims 12 and 60); a retroviral provirus comprising the retroviral vectors (Claims 13, 14, 61, 62); a packaging cell line harboring the retroviral vectors (Claims 16 and 63); an isolated human cell comprising the proviruses (Claims 17 and 64); capsules encapsulating the packaging cell lines (Claims 18, 19, 65 and 66); pharmaceutical compositions thereof (Claims 23-25 and 67-68); and methods for expressing heterologous genes in human cells using the retroviral vectors (Claims 26-36 and 41-52); and methods for treating human mammary carcinoma using the retroviral vectors (Claims 37-40 and 73).

Support for the claim amendments can be found throughout the specification..

#### Priority

The Examiner acknowledges Applicants' claim for foreign priority based on application DK 0976/95 on September 6, 1995 but notes that Applicants have not filed a certified copy of the document.

Applicants are filing concurrently herewith certified copies of DK 0976/95 and PCT/EP96/03922.

#### Specification

The Examiner states that "this application is a 371 of PCT/EP96/03922, not a continuation of PCT/EP96/03922" and requires correction (Office Action, page 2).

Applicants respectfully disagree. On March 5, 1998, Applicants filed PTO form "Utility Patent Application Transmittal" wherein it was clearly stated that the subject application is a continuation of PCT/EP96/03922.

The Examiner states that "[t]here is no brief description of drawing in the specification" (Office Action, page 2).

Applicants respectfully disagree and direct the Examiner's attention to page 10 of the subject application.

#### Rejection of Claim 17 under 35 U.S.C. §101

Claim 17 is rejected under 35 U.S.C. §101. The Examiner states that "Claim 17 encompasses cells contained within human beings, which are not considered patentable subject matter" and suggest amending the claim to recite an "isolated human cell" (Office Action, page 3).

Claim 17 has been amended to recite "an isolated human cell", thereby obviating the rejection.

Rejection of Claims 1-12, 15, 16 and 18-40 under 35 U.S.C. §112, first paragraph

Claims 1-12, 15, 16 and 18-40 are rejected under 35 U.S.C. §112, first paragraph “as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention” (Office Action, page 3). The Examiner states that the “specification fails to provide adequate guidance and data for the treatment of disorders or disease of human mammary cells with the DNA construct, retrovirus, cells and encapsulated cells” . . and show the therapeutic effect of said treatment *in vitro* or *in vivo* (Office Action, page 4). Citing Orkin *et al.*, the Examiner states that the “state of the art of gene therapy at the time of the invention is unpredictable” (Office Action, page 4). Citing Aebischer *et al.*, the Examiner states that the “feasibility of encapsulated cells for the treatment of disorder or disease of human mammary cells is still unknown at the time of the invention” (Office Action, page 5). The Examiner concludes that:

it would have required undue experimentation for one skilled in the art at the time of the invention to have made a DNA construct or a recombinant viral vector comprising at least one therapeutic gene under transcriptional control of the WAP or MMTV regulatory sequences, retroviral particle or cells containing said DNA construct or viral vector, encapsulated cells comprising a core containing said cells to treat disorders or diseases of human mammary cells, including human mammary carcinoma and show therapeutic effect of said treatment *in vivo*. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the absence of working examples and scarcity of guidance in the specification, and the unpredictable nature of the art” (Office Action, pages 6-7).

Applicants respectfully disagree. The first paragraph of § 112 requires nothing more than objective enablement (*In re Marzocchi & Horton* 169 USPQ 367, 369 (CCPA 1971)). In *Marzocchi* the court stated that:

a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. *Id.*

The court further stated that:

it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *Id.* at 370.

In the specification as filed, Applicants teach how to make a retroviral vector comprising a heterologous gene placed under the transcriptional control of an MMTV or WAP promoter and show that the rodent MMTV and WAP regulatory sequences drive expression of the heterologous gene in human mammary gland cells. Based on Applicants' data, it is reasonable to expect that the claimed retroviral vector, and a retroviral vector particle, retroviral provirus, a cell line and/or a capsule harboring the vector can be used (*e.g., in vivo, ex vivo*) to treat disorders or diseases of human mammary cells. The court has clearly stated that a rigorous or an invariable exact correlation is not required (*Cross v. Iizuka* 224 USPQ 739, 747 (Fed. Cir. 1985)). The court has further stated that:

the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the Examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition (*In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995)) (MPEP, 7<sup>th</sup> edition, 2164.02, page 2100-148).

Clearly a person of skill in the art can prepare the claimed retroviral vector and administer the vector to a human cell following the guidance provided in the subject specification as filed (see, for example, the exemplification). In addition, the person of skill in the art would accept Applicants' data as reasonably correlating to expressing a heterologous gene in a human cell (*e.g., Claim 26, Claim 41*) and/or treating human mammary carcinoma (*e.g., Claim 37, Claim 70*)

The Examiner has not provided evidence to show that one skilled in the art would not accept Applicants' *in vitro* data as reasonably correlating to the claimed methods. The Examiner cites the Orkin *et al.* reference as evidence that the "state of the art of gene therapy at the time of the invention is unpredictable" (Office Action, page 4). Orkin *et al.*, however, discuss clinical applications of gene therapy. Clinical data is not a requirement of patentability (*In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995)). Citing Aebischer *et al.*, the Examiner states that the

“feasibility of encapsulated cells for the treatment of disorder or disease of human mammary cells is still unknown at the time of the invention” (Office Action, page 5). Aebischer *et al.* “compared the ability of dopamine-secreting cells, encapsulated by 2 different methods, to reverse experimental Parkinson’s disease” (Aebischer *et al.*, abstract). Aebischer *et al.* teach that their results “raises questions about the in vivo stability of polyelectrolyte-based capsules *implanted in the nervous system*” (Aebischer *et al.*, abstract, emphasis added). This teaching is not an indication that the “feasibility of encapsulated cells for the treatment of disorder or disease of human mammary cells is still unknown at the time of the invention”. Indeed, Aebischer *et al.* teach that “[t]ransplantation of polymer-encapsulated endocrine tissue also allows the release of hormones which are regulated by humoral signals from the host environment” (Aebischer *et al.*, page 178, column 1). Furthermore, Applicants direct the Examiner’s attention to the Shao *et al.* reference, wherein the authors state that their study of encapsulated GM-CSF-secreting cells in semi-permeable microcapsules “demonstrates the merit” of the cell encapsulation system (Shao *et al.*, page 60, column 1). Clearly, the art indicates that, as taught by Applicant, it is feasible to use encapsulated cells to treat a disorder or disease of human mammary cells.

Applicants have provided an enabling disclosure for the full scope of the claimed invention, particularly as amended.

#### Rejection of Claims 1-22 and 26-40 under 35 U.S.C. §112, second paragraph

Claims 1-22 and 26-40 are rejected under 35 U.S.C. §112, second paragraph “as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention” (Office Action, page 7).

The Examiner states that Claims 1-19 “are vague and indefinite because it is unclear how or whether the recitation of the intended use would limit the claimed vector and/or cells” (Office Action, page 7). Claims 1-19 have been amended to remove the use phrase.

The Examiner states that there is no antecedent basis for the term “said viral vector” in Claims 7-9, 12, 21, 24, 34-36 and 38. Claims 7, 8, 21, 34 and 35 have been canceled. The remaining claims have been amended to recite proper antecedent basis.

The Examiner states that it is unclear whether a retroviral provirus alone or a retroviral provirus integrated in the vicinity of the human genome is intended to be claimed in Claim 13. Claim 13 has been amended to delete the phrase “integrated in the human genome”.

The Examiner states that the phrase “such as” in Claims 11 and 32 renders the claim indefinite because it is unclear whether the limitation following the phrase are part of the claimed invention. Claims 11 and 32 have been amended to remove the phrase “such as”.

The Examiner states that Claims 20-22 and 26-36 do not set forth steps involved in the method/process, and therefore, it is unclear what method/process Applicants are intending to claim. Claims 20-22 have been canceled. Claim 26 has been amended to recite the step involved in the claimed method.

The Examiner states that there is no antecedent basis for “said deleted region” in Claim 36. Claim 36 has been amended to recite proper antecedent basis.

The Examiner states that Claims 37-40 recite incomplete methods, *e.g.*, how and where the medicament is to be administered to a human, is the therapeutic gene expressed, is sufficient amount of therapeutic present in target site, and if the therapeutic product present for sufficient duration of time to exhibit therapeutic effect. Claims 37-40 have been amended to indicate that the gene placed under regulatory control of the MMTV promoter is expressed and results in treatment of the mammary carcinoma, and thus, recite complete methods. Furthermore, as pointed out by the court, the meaning of a claim is not analyzed in a vacuum, but in light of the teachings in the specification (*In re Moore and Janoski*, 169 U.S.P.Q. 236, 238 (CCPA 1971)). Applicants clearly teach in the specification as filed that the claimed compositions can be administered to “a wide variety of locations, including, for example, into sites such as an organ or to a site of a tumor . . . administered orally, intravenously, buccal/sublingual, intraperitoneally, or subcutaneously” (specification, page 22, lines 1-6). In addition, Applicants teach that the “daily dosage depends upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician in charge” (specification, page 22, lines 6-11).

The amendments to the claims discussed above obviate the rejection under 35 U.S.C. §112, second paragraph.

Rejection of Claims 1-3 and 6 under 35 U.S.C. §102(b)

Claims 1-3 and 6 are rejected under 35 U.S.C. §102(b) “as being anticipated by Gunzburg *et al.*, 1991 (U) or Velander *et al.*, 1992 (V)” (Office Action, page 9). The Examiner states that “Gunzburg *et al.* produced a plasmid vector containing human growth hormone (hGH) under the control of a WAP promoter for the expression of hGH in transgenic mice” and “Velandar *et al.* constructed a plasmid DNA containing human protein C under the control of WAP promoter for the expression of protein C in transgenic swine” (Office Action, page 9).

Gunzburg *et al.* “used the 5' flanking sequences of the WAP gene to direct the expression of human GH (hGH) to the mammary glands of transgenic mice” (Gunzburg *et al.*, page 123, column 2).

Verlander *et al.* teach a “fusion gene consisting of the cDNA for human protein C inserted into the first exon of the mouse whey acidic protein gene” (Verlander *et al.*, abstract). Verlander *et al.* teach that “the mouse whey acidic protein gene contains regulatory elements that can direct cDNA expression at high levels in the pig mammary gland” (Verlander *et al.*, abstract).

As amended, Claims 1-3 and 6 relate to a retroviral vector comprising a heterologous gene placed under transcriptional control of an MMTV regulatory sequence. Neither Gunzburg *et al.* nor Verlander *et al.* teach use of a MMTV regulatory sequence. Newly added Claims 53-59 relate to a retroviral vector comprising a heterologous gene placed under transcriptional control of an WAP regulatory sequence. Neither Gunzburg *et al.* nor Verlander *et al.* teach use of a retroviral vector comprising a heterologous gene placed under transcriptional control of a WAP regulatory sequence.

Thus, the teachings in Gunzburg *et al.* or Verlander *et al.* do not anticipate the subject matter of Applicants' claimed invention, particularly as amended.

Rejection of Claims 1 and 4-6 under 35 U.S.C. §102(b)

Claims 1 and 4-6 are rejected under 35 U.S.C. §102(b) "as being anticipated by Ricketts et al., 1992(W)" (Office Action, page 9). The Examiner states that "Ricketts et al. constructed a plasmid containing P450c21 gene under the control of MMTV-LTR for the expression of P450c21 in cultured COS-1 cells" (Office Action, page 10).

Using DNA constructs of bacterial origin, Ricketts *et al.* tested four different promoters, the SV40 early and late promoters, MMTV-LTR and CMV immediate early promoter for their ability to drive expression of P450c21 in cultured COS-1 cells (Ricketts *et al.*, abstract).

As amended, Claims 1-3 and 6 relate to a retroviral vector comprising a heterologous gene placed under transcriptional control of an MMTV regulatory sequence. Ricketts *et al.* do not teach use of a retroviral vector comprising a heterologous gene placed under transcriptional control of an MMTV regulatory sequence.

Thus, the teachings of Ricketts *et al.* do not anticipate the subject matter of Applicants' claimed invention, particularly as amended.

Rejection of Claims 1-17 and 23-26 under 35 U.S.C. §103(a)

Claims 1-17 and 23-26 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Dranoff et al., (1993) (U2) in view of Lefebvre et al., 1991 (V2), Paleyanda et al., 1994 (W2) and Meade et al., 1989 (U2), US Pat. No. 4,873,316 (A)" (Office Action, page 10). The Examiner states that Dranoff *et al.* teach subcloning DNA sequences encoding cytokines and adhesion molecules into the retroviral vector MFG which contains the Mo-MuLV LTR and introducing the resulting construct into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells. The Examiner notes that the transduced B16 cells are inoculated into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene, but do not teach using MMTV or WAP promoter for the expression of a gene product in mammary gland. The Examiner cites Lefebvre *et al.* as revealing the presence of MMTV promoter and the positive and negative regulatory regions upstream of the MMTV promoter; Paleyanda *et al.* as teaching construction of a plasmid containing the HPC gene under the control of mouse WAP promoter for making a transgenic mouse expressing HPC and that HPC mRNA is detected mainly in the mammary gland; and Meade *et al.* as teaching production of recombinant protein in mammal's milk by using expression system comprising casein promoter operably linked to desired gene. It is the Examiner's opinion that:



Because it is well known that MMTV and WAP promoter are mammary gland-specific promoter, one would have been motivated to substitute Mo-MLV LTR with MMTV or WAP promoter to combine with any desired gene for the construction of recombinant retroviral vector, recombinant retrovirus, or cells harboring said viral vector, and for the expression of any desired gene product *in vitro*. It would have been obvious for a person of skill at the time of the invention to have practiced the claimed invention with reasonable expectation of success *in vitro* (Office Action, pages 11-12).

Applicants respectfully disagree. As discussed below, that the *rodent* MMTV and WAP regulatory sequences can direct expression of a heterologous gene in *human* cells or that the MMTV and WAP regulatory sequences would do so using a retroviral vector, is not made obvious by the cited prior art.

As amended, Applicants claim a retroviral construct comprising a heterologous gene placed under the transcriptional control of an MMTV regulatory sequence (Claims 1-11) or a WAP regulatory sequence (Claims 53-59); a recombinant retroviral particle produced from the retroviral vectors (Claims 12 and 60); a retroviral provirus comprising the retroviral vectors (Claims 13, 14, 61, 62); a packaging cell line harboring the retroviral vectors (Claims 16 and 63); an isolated human cell comprising the proviruses (Claims 17 and 64); capsules encapsulating the packaging cell lines (Claims 18, 19, 65 and 66); pharmaceutical compositions thereof (Claims 23-25 and 67-68); methods for expressing heterologous genes in human cells using the retroviral vectors (Claims 26-36 and 41-52); and methods for treating human mammary carcinoma using the retroviral vectors (Claims 37-40 and 73).

Dranoff *et al.* generated a variety of recombinant retroviruses encoding different potential immunomodulators and compared the vaccination properties of both live and irradiated tumor cells transduced by the viruses in several different tumor models (Dranoff *et al.*, page 3539, column 2). Dranoff *et al.* show that in B16 melanoma cells, in which nontransduced irradiated cells possess little ability to stimulate systemic anti-tumor immunity, a previously unidentified molecule, murine granulocyte-macrophage CSF (GM-CSF), is the most potent stimulator of systemic anti-tumor immunity of the 10 molecules tested (Dranoff *et al.*, page 3539, column 2). Dranoff *et al.* used the Mo-MuLV LTR to express the 10 molecules in the model (Dranoff *et al.*, Figure 1), and as noted by the Examiner, “do not teach using MMTV or WAP promoter for the expression of a gene product in a mammary gland” (Office Action, page 11).

Using a series of mammary and nonmammary murine cell lines, Lefebvre *et al.* “identified two elements, located upstream of the hormone responsive element, that specifically

regulate the MMTV promoter. Lefebvre *et al.* do not teach or even suggest that the MMTV promoter can be used to express a heterologous gene in a human cell.

Paleyanda *et al.* analyzed the “tissue-specific and developmental pattern of expression of a hybrid gene comprised of mWAP promoter fragment and the human protein C (HPC) gene” in transgenic mice. Paleyanda *et al.* do not teach or even suggest that the WAP promoter can be used to express a heterologous gene in a human cell.

Meade *et al.* teach “the transgenic incorporation of one or more copies of a construct comprising a milk-specific protein promoter or any promoter sequence specifically activated in a mammary tissue, operatively linked to a DNA sequence coding for a desired protein through a DNA sequence coding for a signal peptide that permits the secretion and maturation of the desired recombinant protein in the mammary tissue” in mice (Meade *et al.*, column 2, lines 44-53). In particular, Meade *et al.* introduced a construct in which a casein promoter was operatively linked to tissue plasminogen activator (TPA) into fertilized mouse embryos, implanted the embryos in pseudopregnant female mice and crossbred the progeny to produce transgenic mice that produced TPA in their milk (Meade *et al.*, Example 3). Meade *et al.* teach that the MMTV LTR can be used to produce a recombinant protein in the mammary tissue of mice, but do not teach or even suggest that the MMTV promoter can be used to express a heterologous gene in a human cell.

Where the claimed invention is rejected as obvious in view of a combination of references, § 103 requires both (1) that “the prior art would have suggested to the person of ordinary skill in the art that they should . . . carry out the claimed process”; and (2) that the prior art should establish a reasonable expectation of success (*In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). “Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant’s disclosure.” *Id.* The court has clearly stated that

[a]n invention is not obvious merely because it is a combination of old elements each of which was well known in the art at the time the invention was made. . . . Rather, if such a combination is novel, the issue is whether bringing them together as taught by the patentee was obvious in light of the prior art. . . . The critical inquiry is whether ‘there is something in the prior art as a whole to *suggest* the desirability, and thus obviousness of making the invention’ (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* 13 USPQ2d 1737 at 1765).

That is, the issue is “whether the teachings of the prior art would, *in and of themselves and without the benefit of appellant’s disclosure*, make the invention as a whole, obvious” (*In re Spinnoble* 160 USPQ237 at 243 (CCPA 1969)).

There are no teachings in the art cited which, in and of themselves, would direct the skilled person to obtain expression of a heterologous gene in human cells using the rodent MMTV and WAP regulatory sequences or use a retroviral vector to do so. MMTV and WAP are rodent regulatory sequences and the cited art provides no suggestion or expectation of success that these rodent regulatory sequences can direct expression of a heterologous gene in human cells. As indicated in the specification, the WAP gene “is only expressed in the pregnant and lactating mammary glands of rodents and has no human homologue. . . and “[i]t is therefore not predictable that this regulatory element will function at all to direct expression in human mammary cells and/or allow expression in human mammary carcinoma cells” (specification, page 2, lines 19-25; see also Gunzburg *et al.*, page 123, column 2).

Dranoff *et al.* do not teach using MMTV or WAP promoter for the expression of a gene product. Thus, the teachings in the Dranoff *et al.* reference are not relevant to Applicants’ invention. Lefebvre *et al.* identified two region of the MMTV LTR that regulate its promoter activity in murine cells, but do not teach or even suggest that the MMTV promoter can be used to express a heterologous gene in a human cell. Paleyanda *et al.* teach a hybrid gene comprised of mWAP promoter fragment and the human protein C (HPC) gene which was used to express HPC in transgenic mice, but do not teach or even suggest that the WAP promoter can be used to express a heterologous gene in a human cell. Meade *et al.* teach introduction of a construct in which a casein promoter was operatively linked to tissue plasminogen activator (TPA) into transgenic mice which produced HPC in their milk, and that the MMTV LTR can be used to direct expression of a recombinant protein in the mammary tissue of mice. However, Meade *et al.* do not teach or even suggest that the MMTV promoter can be used to express a heterologous gene in a human cell. Clearly, the combined teachings of the cited references, either alone or in combination, do not teach or even suggest expression of a heterologous gene in human cells using the rodent MMTV and WAP regulatory sequences.

Furthermore, the cited references do not teach or suggest inserting the WAP or MMTV regulatory sequences into a retroviral vector and to introduce such a vector into a human mammary cell. As indicated in the Hejnar *et al.*, *Virology*, 255:171-181 (1999) reference, a copy of which is being filed concurrently as Exhibit A, transcription of a provirus, *i.e.*, of recombinant retroviral vectors integrated into the host cell genome, is regularly suppressed. This was found, for example, for avian endogenous proviruses, in cells infected with MoMLV and in cells infected with HIV-1. Such inhibition is either due to methylation of provirus-DNA, specifically

of the LTR, and thus, of the promoter region or because the provirus fails to integrate into a favorable site for transcription. Applicants also direct the attention to the abstract, Fincham *et al.*, *J. Virol.*, 65:461-463 (1991), which is being concurrently herewith as Exhibit B. Furthermore, in the Akroyd *et al.*, *Oncogene*, 1:347-354 (1987) reference, a copy of which is being filed as Exhibit C, the authors found that flanking cellular elements can act over several kilobases to inhibit provirus transcription. Finally, Applicants direct the Examiner's attention to the Ricketts *et al.* reference wherein the authors teach that inclusion of the MMTV into a DNA construct of bacterial origin does not or, only to a low extent, drive expression of a heterologous gene in COS-1 cells, which are derived from African green monkey. Thus, the art clearly indicates that Applicants' finding of integration of a heterologous gene with the WAP promoter into the human genome, and thus, present in a provirus, resulted in transcription and expression of the heterologous gene in human cells is a surprising result.

The prior art combination of record has been made with the impermissible advantage of hindsight, and thus, the rejection is legally improper. That is, in making the obviousness rejection, the Examiner has read the prior art with the benefit of Applicant's disclosure in which there is a clear teaching that the rodent MMTV and WAP regulatory sequences can direct expression of a heterologous gene in human cells and that the MMTV and WAP regulatory sequences would do so using a retroviral vector. As the court made clear in *In re Dow*, it is not legally correct to rely on Applicant's disclosure for the suggestion that the cited references should be combined and the expectation of success. In the present case, the suggestion or motivation for combining the references and the expectation of success are not found in the prior art, but rather in Applicant's disclosure.

The combined teachings of Dranoff *et al.* in view of Lefebvre *et al.*, 1991, Paleyanda *et al.* and Meade *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

#### Rejection of Claims 1-19 and 23-36 under 35 U.S.C. §103(a)

Claims 1-19 and 23-36 are rejected under 35 U.S.C. §103(a) "as being unpatentable over Shao *et al.*, 1994 (X2) and Dranoff *et al.* 1993 (U2) in view of Lefebvre *et al.*, 1991 (V2) and Paleyanda *et al.*, 1994 (W2)" (Office Action, page 12). The Examiner states that Shao *et al.* encapsulated B16-F10 cells transduced with retrovirus containing GM-CSF gene and monitored the secretion of GM-CSF in the culture medium. The Examiner states that Dranoff *et al.* teach

subcloning DNA sequences encoding cytokines and adhesion molecules into the retroviral vector MFG which contains the Mo-MuLV LTR, introducing the resulting construct into CRIP packaging cells to generate recombinant virus which are used to transfect B16 melanoma cells and inoculating the transduced B 16 cells into C57BL/6 mice to monitor the delay of tumor formation associated with the synthesis of cytokine transgene. The Examiner notes that Shao *et al.* and Dranoff *et al.* do not teach using MMTV or WAP promoter for the expression of a desired gene. The Examiner cites Lefebvre *et al.* as revealing the presence of MMTV promoter and the positive and negative regulatory regions upstream of the MMTV promoter; and Paleyanda *et al.* as teaching construction of a plasmid containing the HPC gene under the control of mouse WAP promoter for making transgenic mouse expressing HPC and that HPC mRNA is detected mainly in the mammary gland. The Examiner concludes that:

It is well known that MMTV and WAP promoter are mammary gland-specific promoter, one would have been motivated to substitute Mo-MuLV LTR with MMTV or WAP promoter to combine with a desired gene for the construction of recombinant retroviral vector, recombinant retrovirus, cells harboring said viral vector, and encapsulated cells for the expression of said desired gene product. It would have been obvious for a person of ordinary skill at the time of the invention to have combined the teaching of the references set forth above and have practiced the claimed invention with reasonable expectation of success *in vitro* (Office Action, page 13).

Applicants respectfully disagree. That the combined teachings of Dranoff *et al.*, Lefebvre *et al.* and Paleyanda *et al.* do not render obvious Applicants' claimed invention, particularly as amended has been discussed above. Shao *et al.* do not provide what is lacking in these references to render obvious Applicants' claimed invention.

Shao *et al.* studied whether prolonged delivery of GM-CSF can be achieved by encapsulating GM-CSF-secreting cells in semi-permeable micorcapsules (Shao *et al.*, page 59, column 1). Based on their results, Shao *et al.* teach that their study "demonstrates the merit of this cell encapsulation system" and "suggests an alternative mode of cytokine delivery and provides basis for other cell-based artificial organ designs" (Shao *et al.*, page 60, column 1). As discussed above, that the *rodent* MMTV and WAP regulatory sequences can direct expression of a heterologous gene in *human* cells or that the MMTV and WAP regulatory sequences would do so using a retroviral vector, is not made obvious by the combined teachings of the Dranoff *et al.*, Lefebvre *et al.* and Paleyanda *et al.* references. Shao *et al.* do not discuss use of the MMTV or WAP regulatory sequences for any purpose.

Thus, the combined teachings of Shao *et al.* and Dranoff *et al.* in view of Lefebvre *et al.* and Paleyanda *et al.* do not render obvious Applicants' claimed invention, particularly as amended.

#### CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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